in cancer patients who have been treated with exogenous interferon gamma or interleukin 2.[4] The latter is a cytokine which produces significant eosinophilia.[5] Thus, in all likelihood the abnormal tryptophan metabolism seen in EMS patients is a consequence of the immune activation in this disease rather than the cause of it. Indeed, one might reason that an important factor in the pathogenesis of EMS may be an excess, rather than a deficit of interferon gamma. The observed active catabolism of tryptophan by the IDO pathway may well lead to a deficiency of tryptophan and serotonin. If serotonin does play a role in down-regulating interferon production as suggested,[6] this deficit of serotonin may lead to an unchecked increase in interferon gamma and result in excessive activation of macrophages and eosinophils as seen in EMS.

In addition, although tryptophan metabolism may play a role in the pathogenesis of EMS, epidemiologic studies point increasingly to a contaminant as the principal causal factor.[7-9] The recent identification of the chemical structure of one such contaminant[10] may soon lead to animal and in vitro models which will permit dissection of this most interesting syndrome.

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Drs Criswell and Sack Respond

To THE EDITOR: We are pleased to respond to the thoughtful comments of Drs Hertzman and Brown. No one has measured interferon-gamma (IFN-γ) levels in patients with the eosinophilia-myalgia syndrome (EMS); thus, the finding by Silver and co-workers of elevated serum levels of L-kynurenine and quinolinic acid in such persons is unexplained.[1]

Interferon gamma can indeed stimulate indoleamine-2,3-dioxygenase (IDO), the rate limiting enzyme of the kynurenine pathway of L-tryptophan metabolism, but other substances such as endotoxin can also induce this enzyme. Furthermore, L-tryptophan influences the ability of IFN-γ to induce IDO.

Products of the indoleamine pathway of L-tryptophan metabolism, serotonin and melatonin, inhibit the production of IFN-γ. This may be important in the pathogenesis of EMS because IFN-γ is known to inhibit synthesis of collagen, the production of interleukins 4 and 5, and the production of IgE by B lymphocytes.[2-5]

It is likely that most, if not all, of the current cases of EMS are associated with a contaminant generated during the manufacturing of L-tryptophan. The manner in which L-tryptophan or a contaminant induces EMS is still open to speculation, however.

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